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Bidirectional relationship between eating disorders and autoimmune diseases

Anna Hedman, Ph.D.[1], Lauren Breithaupt, M.A.[1,2], Christopher Hübel, M.D., M.Sc.,[1,3] Laura M. Thornton, Ph.D.[4], Annika Tillander, Ph.D.[1,5], Claes Norring, Ph.D.[6], Andreas Birgegård, Ph.D.[6], Henrik Larsson, Ph.D.[1,7], Jonas Ludvigsson, M.D., Ph.D.[1,8], Lars Sävendahl, M.D., Ph.D.[9], Catarina Almqvist, M.D., Ph.D.[1,10], Cynthia M. Bulik, Ph.D.[1,4,11]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

[2]Department of Psychology, George Mason University, Fairfax, VA, USA

[3]Social, Genetic & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK

[4]Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC

[5]Department of Computer and Information Science, Linköping University, Linköping, Sweden

[6] Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, & Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden

[7]School of Medical Sciences, Örebro University, Örebro, Sweden

[8]Department of Pediatrics, Örebro University Hospital, Örebro, Sweden

[9]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

[10]Pediatric Allergy and Pulmonology Unit, Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

[11]Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, NC

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Abstract

Background: Immune system dysfunction may be associated with eating disorders, and associations may have implications for detection, risk assessment, and treatment of both autoimmune diseases and eating disorders. However, the nature of the relationship between these two disease entities remains unclear. We evaluated the strength of associations for the bidirectional relationships between eating disorders and autoimmune diseases. **Methods:** In this nationwide population-based cohort study, Swedish registers were linked to establish a cohort of over two and a half million individuals born in Sweden between January 1, 1979 and December 31, 2005 and followed-up until December 2013. Two Cox proportional hazard regression models were used to investigate 1) subsequent risk of eating disorders in individuals with autoimmune diseases and 2) subsequent risk of autoimmune diseases in individuals with eating disorders. **Results:** We observed a strong, bidirectional relationship between the two classes of illness indicating that diagnosis of one illness increased the risk of the other. In women, autoimmune disease exposure increased subsequent hazard of anorexia nervosa, bulimia nervosa, and other eating disorders. Likewise, anorexia nervosa, bulimia nervosa, and other eating disorders increased subsequent hazard of autoimmune diseases. The gastrointestinal-related autoimmune diseases celiac and Crohn's showed a bidirectional relationship with anorexia nervosa and other eating disorders. Psoriasis showed a bidirectional relationship only with other eating disorders. Prior type 1 diabetes increased risk for anorexia nervosa, bulimia nervosa, and other eating disorders. In men, we did not observe a bidirectional pattern, but prior autoimmune arthritis increased risk for other eating disorders. **Conclusions:** The associations between eating disorders and autoimmune diseases provide support for previously reported associations and the bidirectional risk pattern observed suggests either a shared underlying mechanism or a third explanatory variable contributing to the association of these illnesses.

Keywords: hazard, risk, immune system, cox regression, anorexia nervosa, bulimia nervosa, autoimmunity

Introduction

Autoimmunity has been implicated in several psychiatric disorders (Barbuti et al., 2017; Eaton et al., 2006; Edmiston, Ashwood, & Van de Water, 2017; Frick & Pittenger, 2016; Mechawar & Savitz, 2016; Muskens, Velders, & Staal, 2017; Neigh & Ali, 2016; Tylee et al., 2017; Volk, 2017; see eTable 1 for a review), including eating disorders (Raevuori et al., 2014; Wotton, James, & Goldacre, 2016; Zerwas et al., 2017). Moreover, the first genome-wide significant association in anorexia nervosa (AN) was identified (Duncan et al., 2017) in a region previously implicated in autoimmune diseases, including type 1 diabetes (Barrett et al., 2009) and arthritis (Okada et al., 2014).

Eating disorders and autoimmunity are complex traits influenced by numerous genetic variants acting additively in combination with environmental factors to influence phenotypic expression (Yilmaz, Hardaway, & Bulik, 2015). Autoimmunity varies on a continuum, ranging from no clinical consequences to pathogenic autoimmunity causing inflammatory organ infiltration, tissue damage, and overt disease-specific symptomatology. Autoimmune diseases occur in ~7-9% of the population and increase with age (Theofilopoulos, Kono, & Baccala, 2017).

Extensive Swedish health registers afforded an exploration of bidirectional associations between eating disorders and autoimmune diseases (eTable 2). We extended prior studies (Raevuori et al., 2014; Wotton et al., 2016; Zerwas et al., 2017) by examining a cohort of more than 2.5 million individuals.

Methods

Study Population and Data Sources

We studied individuals aged 0-35 years born in Sweden between January 1, 1979 and December 31, 2005, excluding those who emigrated or died before age 8, or were from multiparous births, to reduce nesting. Individuals were followed until eating disorder onset, autoimmune disease onset, death, emigration from Sweden, or the end of the follow-up period (December 31, 2013), whichever came first. We linked registers using the national personal identification number (Ludvigsson, Otterblad-Olausson, Pettersson, & Ekbom, 2009). Consistent with prior research (Mårild et al., 2017; Mustelin et al., 2017; Yao et al., 2016), birth year and sex were from the Total Population Register (Ludvigsson et al., 2016); migration data were from the Migration Register (Statistics Sweden); causes of death were from the Cause of Death Register (Statistics Sweden); and socioeconomic status (SES) was estimated using highest parental education (i.e., completed year 9 or below; completed year 12; >2 years tertiary) from the Longitudinal Integration Database for Health Insurance and Labour Market Studies (Statistics Sweden, 2012) when the child was 8 years old. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

Eating Disorder Outcomes

Eating disorder diagnoses were from the National Patient Register (NPR), which tracks all inpatient care since 1987 and outpatient care since 2001 (Ludvigsson et al., 2011; Center for Epidemiology at the National Board of Health and Welfare, n.d.); Riksät-National Quality Register for Treatment for Eating Disorders (since 1999) (Emilsson, Lindahl, Köster, Lambe, & Ludvigsson, 2015); the regional quality assurance system for eating disorders, Stepwise (since 2005; Birgegård, Björck, & Clinton, 2010); and the clinical database for child and adolescent psychiatry in Stockholm, Pastill (since 2001; Lindevall, 2009). NPR discharge diagnoses were from Swedish ICD-9 and ICD-10 (Smedby, 2006). In Riksät and Stepwise, eating disorder

diagnoses were based on *DSM-IV-TR* (American Psychiatric Association, 2005) (Birgegård et al., 2010). Coverage in Riksät and Stepwise has increased over time (Javaras et al., 2015). Pastill eating disorder diagnoses were based on ICD-10 or DSM-IV from Child and Adolescent Mental Health Services in Stockholm County (Lindevall, 2009).

Four eating disorder outcomes were evaluated: 1) AN: 307B (Swedish ICD-9); F50.0 or F50.1 (ICD-10); or DSM-IV AN or atypical AN; 2) Other eating disorders: 307F (Swedish ICD-9); F50.2, F50.3, or F50.9 (ICD-10); or DSM-IV bulimia nervosa (BN), atypical BN, binge-eating disorder (BED), or eating disorder not otherwise specified (EDNOS). 3) Any eating disorder: included all individuals with an AN, BN, and/or other eating disorder diagnosis. Consistent with previous reports (Allen, Byrne, Oddy, & Crosby, 2013; Stice, Marti, & Rohde, 2013), many individuals had both AN and other eating disorders (at different times) and are included as incident cases for both the AN and other eating disorder outcomes. Thus, the number of incident cases of AN and/or other eating disorders is greater than the number of incident cases of any eating disorder, where each individual can be an incident case only once. Analysis of any eating disorder provide information on the overall incidence of eating disorders without inflation due to diagnostic crossover. 4) BN: included all individuals who received a BN diagnosis in the NPR (F50.2, F50.3) since 1997 or in Riksät, Stepwise, or Pastill. Analyses of BN are considered secondary because the years of observation are fewer than for the other diagnostic groups. BED and EDNOS could not be separated because Swedish ICD-9 only included a heterogeneous category (eating disorders other than AN) and F50.8, from ICD-10, was not consistently used to code BED prior to DSM-5.

Age of onset reflects first contact with the respective diagnosis in the NPR, Riksät, Stepwise, or Pastill after the 8th birthday. The minimum age of onset for eating disorders was 8 to avoid diagnostic misclassification (e.g., childhood feeding difficulties; N excluded=4,493).

Autoimmune Disease Outcome

Autoimmune disease diagnoses were obtained from the NPR using Swedish ICD revisions 8-10 diagnoses based on year of diagnosis. We evaluated any autoimmune disease as a group, and by specific categories: celiac disease, Crohn's disease, ulcerative colitis, psoriasis, arthritis, lupus, and type 1 diabetes (eTable 2). Age of onset was age at first contact with the respective diagnosis in the NPR with no minimum age of onset.

Statistical Analyses

Data management was conducted with SAS version 9.4; analyses were conducted with STATA version 14. False discovery rate (FDR) corrections were made for each predefined set of hypothesis tests (n=128) (Benjamini & Hochberg, 2000; Glickman, Rao, & Schultz, 2014).

To optimize our longitudinal data, we performed two sets of Cox proportional hazard regression models estimating the relative hazards of eating disorders following autoimmune disease exposure and autoimmune disease risk following eating disorder exposure. In the first set, autoimmune disease status (presence/absence) was treated as time-dependent exposure and calendar year (1987-1996, 1997-2006, 2007-2013) was adjusted for as a time varying variable; all other variables were considered time-independent. For each analysis, we estimated hazard ratios (HR) for eating disorders in individuals exposed to an autoimmune disease compared to those not exposed. In the second set of analyses, we estimated HRs for autoimmune diseases, comparing individuals exposed to an eating disorder to those not exposed, with eating disorder status as a time-varying exposure variable. All estimates were adjusted for calendar-time in the parametric part of the Cox model, and for age in the nonparametric part. SES was entered as a covariate into all models. In Cox models, HRs greater than 1 indicate a higher risk of illness, whereas HRs less than 1 indicate a lower risk of illness compared with unaffected individuals. Analyses were applied to males and females separately.

Significantly increased HRs, after FDR correction, for an autoimmune disease after eating disorder exposure were investigated for effects of temporal proximity by calculating HR for ≤1 year, >1 year to ≤4 years, and >4 years between exposure and outcome. Due to possible misdiagnosis of eating disorders before age 8, we did not explore temporal proximity between autoimmune disease exposure and eating disorder onset. Furthermore, we did not investigate different ages of eating disorder onset as age of onset distributions revealed no evidence of bi- or multimodal patterns justifying such an approach, rendering any age at onset cutoff arbitrary (Figures 1a and 1b).

Results

Our cohort comprised 2,545,611 individuals (51.4% males, 48.6% females) followed over 33,640,644 person-years (range: 1 month to 22 years).

Sample characteristics

Table 1 presents prevalence and age at first diagnosis. Eating disorders occurred more commonly in females (2.0%) than in males (0.1%): 94% of eating disorder cases were female.

The most common autoimmune diseases were celiac disease, type 1 diabetes, and psoriasis. A higher percentage of females than males were diagnosed with an autoimmune disease.

Risk of Eating Disorders Following Exposure to Autoimmune Disease

Tables 2a and 2b provide the results from the Cox regression models estimating HRs of eating disorders after an autoimmune disease exposure in males and females, respectively. The following sections only present significant results.

In males, any preceding autoimmune disease was associated with an 82% increased hazard in other eating disorders, a 78% increased hazard in any eating disorder, and a 56% increased hazard for BN. In females, any preceding autoimmune disease increased the hazard for AN by 59%, for other eating disorders by 71%, for any eating disorder by 62%, and for BN by 57%.

We also evaluated the risk for subsequent eating disorders following exposure to celiac disease, Crohn's disease, ulcerative colitis, psoriasis, arthritis, lupus, and type 1 diabetes. In males, exposure to arthritis increased the risk for other eating disorders by 357% and any eating disorder by 267%, however, the assumption of proportional hazards was violated. In females, the risk for subsequent AN was increased after celiac disease (50%), Crohn's disease (89%), and type 1 diabetes (71%). Moreover, celiac disease (47%), Crohn's disease (63%), ulcerative colitis (52%), psoriasis (33%), and type 1 diabetes (153%) increased risk for subsequent other eating disorders. Risk for any eating disorder was increased after exposure to celiac disease (45%), Crohn's disease (61%), ulcerative colitis (49%), psoriasis (27%), and type 1 diabetes (119%). Risk for subsequent BN was increased by 222% by an earlier diagnosis of type 1 diabetes.

Risk of Autoimmune Disease Following Exposure to an Eating Disorder

Tables 3a and 3b provide the results from the Cox regression models estimating risk for subsequent autoimmune disease following exposure to an eating disorder in males and females. After correcting for multiple testing, we did not observe an increased risk for autoimmune diseases after eating disorder exposure in men. However, females with AN (42%), other eating disorders (58%), any eating disorder (53%), or BN (48%) were at increased risk for later autoimmune diseases.

We evaluated the risk for celiac disease, Crohn's disease, ulcerative colitis, psoriasis, arthritis, lupus, and type 1 diabetes following a diagnosis of AN, other eating disorders, any

eating disorder, or BN in males and females. Males diagnosed with eating disorders did not show an increased risk for subsequent autoimmune diseases after correcting for multiple testing. In females, prior exposure to AN (83%), other eating disorders (69%), and any eating disorder (72%) increased risk for celiac disease. Other eating disorders (72%) and any eating disorder exposure (63%) showed increased risk for Crohn's disease. Exposure to other eating disorders increased the risk for subsequent psoriasis by 38%.

Temporal Proximity of Risk of Autoimmune Disease Following Exposure to an Eating Disorder

We explored effects of temporal proximity between exposure to eating disorders and risk for autoimmune disease in females (eTable 3) as only females had significant findings. Exposure to AN was associated with an increased risk (105%) of being diagnosed with any autoimmune disease within the first year after AN diagnosis and with a 49% increased risk between years 1 and 4. Similarly, risk for celiac disease was increased 217% within the first year and 84% in years 1 to 4 after AN diagnosis. The exposure to other eating disorders increased the risk of being diagnosed with any autoimmune disease for all three time periods: 216% for 1 year after diagnosis; 47% for 1 to 4 years between diagnoses; and 45% for >4 years. Other eating disorders increased the risk of being diagnosed with celiac disease (165%) and Crohn's disease (188%) within the first year. The increased risk for celiac disease persisted between 1 year and 4 years at 55%. Within the first year, females with any eating disorder were at 114% increased risk of developing any autoimmune disease; 48% increased risk between years 1 and 4; and 32% increased risk >4 years. Any eating disorder increased the risk for celiac disease and Crohn's disease within the first year after diagnoses by 189% and 202%, respectively. The risk of being diagnosed with celiac disease persisted between years 1 and 4 at 58%. BN was associated with a 79% increased risk for any autoimmune disease after 4 years of BN diagnosis.

Discussion

With 2.5 million participants and over 26,000 individuals diagnosed with an eating disorder, to our knowledge, this is the largest prospective register-based study examining the bidirectional associations between autoimmune diseases and eating disorders. Consistent with previous research, we observed positive and strong associations between eating disorders and autoimmune diseases that are on par with reported associations in epidemiological investigations between autoimmune diseases and other psychiatric disorders, such as attention-deficit/hyperactivity disorder (Nielsen, Benros, & Dalsgaard, 2017), depression (Andersson et al., 2015; Euesden, Danese, Lewis, & Maughan, 2017), and schizophrenia (Benros et al., 2014; Chen et al., 2012). We extended previous observations by investigating a variety of autoimmune diseases previously associated with eating disorders in case reports, clinical samples, and smaller cohort studies (Wotton et al., 2016). Our results replicate bidirectional risk patterns of eating disorders and autoimmune diseases explored in two clinical cohort studies (Raevuori et al., 2014; Wotton et al., 2016) and a Danish national study (Zerwas et al., 2017).

In men, we did not observe any bidirectional patterns. Preceding autoimmune arthritis and type 1 diabetes increased the risk for other eating disorders and preceding autoimmune arthritis increased the risk for any eating disorder. The UK study also observed a significantly increased risk for BN in males with type 1 diabetes based on reports from five cases (Wotton et al., 2016).

In women, AN showed a bidirectional relationship with celiac disease, replicating reported results (Mårild et al., 2017; Wotton et al., 2016). Crohn's disease increased risk for AN (Raevuori et al., 2014; Wotton et al., 2016), but was not bidirectionally associated (Wotton et al., 2016). The gastrointestinal-related autoimmune diseases celiac and Crohn's showed a bidirectional relationship with other eating disorders. The Finnish study (Raevuori et al., 2014)

showed increased odds for Crohn's disease and BN, whereas the UK study (Wotton et al., 2016) found an increased risk for celiac disease after BN. Ulcerative colitis increased risk for other eating disorders. Additionally, psoriasis showed a bidirectional relationship with other eating disorders, replicating findings from the UK study (Wotton et al., 2016) and clinical case reports (Basavaraj, Navya, & Rashmi, 2011; Crosta et al., 2014; Ferreira, Abreu, Reis, & Figueiredo, 2016). Type 1 diabetes increased risk for AN, other eating disorders, and BN as previously reported (Raevuori et al., 2014; Wotton et al., 2016); however, Wotton et al. (2016) reported an increased risk for type 1 diabetes after AN and BN which we did not replicate.

The bidirectional nature of some associations suggests either a shared underlying mechanism or a third explanatory variable that influences risk for both disease groups. Such risk-elevating factors could be genetic, environmental, or a combination of both. Current evidence suggests that dysregulated immune function may be one shared underlying mechanism. Several biological factors influencing immune function are described to be predominant or altered in eating disorders: a female preponderance (Chowen, Argente-Arizón, Freire-Regatillo, & Argente, 2017; Klein & Flanagan, 2016; McCarthy, Nugent, & Lenz, 2017), metabolic changes mediated by adipokines such as leptin and adiponectin (Abella et al., 2017; de Candia et al., 2017; Nikolajczyk, Jagannathan-Bogdan, Shin, & Gyurko, 2011; Saucillo, Gerriets, Sheng, Rathmell, & Maciver, 2014), elevated cytokines (Solmi et al., 2015), abnormal levels of estrogen (Khan & Ansar Ahmed, 2015; Klump, Culbert, & Sisk, 2017), and lower abundance or diversity of intestinal microbiota (Carr, Kleiman, Bulik, Bulik-Sullivan, & Carroll, 2016; Kleiman et al., 2015; Lam, Maguire, Palacios, & Caterson, 2017; Postler & Ghosh, 2017; Rooks & Garrett, 2016). These factors potentially influence the relationship between eating disorders and autoimmunity. For example, cortisol levels are dysregulated in eating disorders (Monteleone et al., 1999) possibly due to an altered stress response. Cortisol is often included in the therapeutic

regimen for autoimmune diseases (Ilzarbe et al., 2017; Straub & Cutolo, 2016). Furthermore, Fetissov et al. detected autoantibodies against appetite-regulating peptides, including α-Melanocyte-stimulating hormone and adrenocorticotropic hormone in AN and BN (Fetissov et al., 2002, 2005, 2008). However, the role of autoantibodies in autoimmune diseases is not fully understood. Antibodies may be an epiphenomenon or have a causal effect facilitating aberrant immune cell function leading to cytotoxicity.

Recent research suggests a genetic overlap between several autoimmune diseases and psychiatric disorders; however, the only study to date that has included eating disorders revealed no significant genetic associations between AN and autoimmune diseases or traits (Tylee et al., 2017). The increased risk for eating disorders after type 1 diabetes could be metabolically mediated through a dysregulation of insulin homeostasis, administration of mandatory external insulin, and insulin misuse (Bryden et al., 1999; Colton et al., 2015; Colton, Olmsted, Daneman, Rydall, & Rodin, 2004). Similarly, increased risk of any eating disorder after ulcerative colitis could be due to symptom- and therapy-related behavioral changes as treatment often includes dietary changes and a colectomy with pouches or stoma (Ungaro, Mehandru, Allen, Peyrin-Biroulet, & Colombel, 2017). Patients suffering from inflammatory bowel disease often report eating behavior changes related to their disease, and many perceive food as a risk factor for relapse decreasing their pleasure in eating (Zallot et al., 2013). Moreover, the increased risk of being diagnosed with a gastrointestinal-related autoimmune disease within the first year of having been diagnosed with an eating disorder may suggest diagnostic uncertainty due to the overlap in their clinical presentation complicating the differential diagnosis (Golden & Park, 2017; Ilzarbe et al., 2017; Tokatly Latzer et al., 2018).

Environmental factors, such as diet, dietary behavior, and smoking, also influence the human immune system. Starvation and food restriction (as seen in AN) could reduce

inflammation and attenuate symptoms in autoimmune illnesses (Hafström, Ringertz, Gyllenhammar, Palmblad, & Harms-Ringdahl, 1988). For gastrointestinal-associated immune diseases, dietary changes are often prescribed to control pain, diarrhea, and bleeding (Lane, Zisman, & Suskind, 2017). All of these processes may be active, and the inclusion of genetic, biological, and environmental confounders, as well as a developmental perspective in prospective studies are needed to further clarify the relationships between eating disorders and autoimmune diseases.

Strengths and Limitations

Study strengths include the total-population design and substantially more eating disorder cases than in previous studies (Mårild et al., 2017; Raevuori et al., 2014; Wotton et al., 2016; Zerwas et al., 2017). Prospectively collected data allowed us to explore bidirectional risk and minimized the risk of recall bias since data were routinely collected blind to the hypothesis of this study. For most chronic diseases in the inpatient register, the positive predictive value was found to differ between diagnoses in the NPR and medical journals, but is generally 85-95% (Ludvigsson et al., 2011). In addition, we investigated specific autoimmune diseases, which can inform disease detection, treatment, and management.

The observed bidirectional relationships contribute to evidence of immune system involvement in some subtypes of eating disorders. However, we cannot entirely rule out misdiagnosis or surveillance bias given symptom overlap, especially with gastrointestinal autoimmune diseases. Despite the large sample size and follow-up period, some autoimmune disease risk periods remain outside study timeline (e.g., rheumatoid arthritis age of onset is typically after age 44; Symmons, 2002) and exact ages of onset for diseases cannot be traced in register data. Moreover, although the study covers the peak age of onset for eating disorders

(Javaras et al., 2015), individuals remain at risk across the lifespan. A longer follow-up period could alter some of the bidirectional relationships. Additionally, we were unable to evaluate the associations of BED because it could not be distinguished from other eating disorders in the NPR. The small number of male eating disorder cases limited our investigation of sex differences. Given the large sample size, small differences in prevalence between the sexes would be statistically significant, but their clinical significance questionable. Furthermore, the assumptions of proportional hazards were violated in some of the associations (Tables 2-3). Lastly, the Swedish versions of ICD-8 and ICD-9 could not distinguish between type 1 diabetes and type 2 diabetes; however, as our cohort is young (≤34 years), most individuals with ICD-8 or ICD-9 diabetes are assumed to have type 1 diabetes. Diabetes diagnoses according to ICD-10, the largest proportion in our cohort, are classified into type 1 or type 2.

Conclusions

Results clarify the bidirectional relation between eating disorders and autoimmune processes. Clinically, our results encourage vigilance for the emergence of these illnesses in afflicted individuals. As the size of genomic investigations of both eating disorders and autoimmune diseases increases, we will be well positioned to further explore the extent to which shared genetic factors influence risk for both classes of illness. Identifying common environmental risk factors although less tractable, may also be facilitated by the identification of risk variants or profiles.

Key Points

- In the largest prospective register-based study to date on eating disorders and autoimmune diseases, we replicated strong bidirectional relationships between eating disorders and various autoimmune diseases.
- The observed positive and strong associations between eating disorders and

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Correspondence to: Dr. Bulik, Department of Psychiatry, University of North Carolina at Chapel Hill, CB #7160, 101 Manning Drive, Chapel Hill, NC 27599-7160, USA; tel: +46-8-524 800 00, e-mail: cbulik@med.unc.edu

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